

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

REMARKS

Claims 40, 45 and 48-49 are now pending. Claim 40 has been allowed and Claims 45 and 48-49 are rejected.

Specifically, on page 2 of the Office Action, the Examiner maintains the rejection of Claims 45, 48 and 49 under 35 U.S.C. § 103 as being unpatentable over Gjertsen, in view of Hofmann et al and Jastorff et al for the reasons of record.

On pages 2-3 of the Office Action, the Examiner notes Applicants' arguments that Hofmann et al does not indicate how the teachings therein would relate to the treatment of diseases. However, it is the Examiner's position that the present claims are not directed to the treatment of diseases, and therefore this argument is not persuasive.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Contrary to the Examiner's contention, the claims are directed to treatment of disease, i.e., Claim 45 refers to enhancing T cell proliferation "in a subject in need thereof". Clearly, a subject in need of enhancement of T cell proliferation is one who is afflicted with a disease. This *in vivo* use is not taught or suggested in Hoffmann et al.

Nonetheless, in order to advance prosecution, Applicants hereby amend Claim 45 to refer to a subject having HIV or AIDS. A subject with these T cell diseases would clearly be in need of enhancement of T cell proliferation. Support for this amendment can be found, *inter alia*, in original Claim 21.

On page 3 of the Office Action, the Examiner notes Applicants' argument that Hofmann et al does not teach the

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

specific inhibitors of the PKA I α pathway as claimed. However, it is the Examiner's position that specific inhibitors of the PKA I α pathway are not recited in the rejected claims.

Applicants respectfully submit that the Examiner's position is not well-placed. Claims 48 and 49 do recite specific inhibitors. Further, the class of inhibitors recited in Claim 45 is quite small, and do not encompass the compound taught in Hofmann et al.

Applicants also note that the Examiner contends that the instant claims do not recite activity in the PKA I α pathway.

However, Claim 45 recites that the cAMP analog binds to an RI α subunit and acts as an antagonist. This is inherently activity in the PKA I α pathway.

Nonetheless, in order to advance prosecution, Applicants hereby amend Claim 45 to refer to a pharmaceutically effective amount of "a specific inhibitor of PKA RI α ₂C₂ isozyme, wherein said inhibitor is a cAMP antagonist and is a thio-substituted cAMP analog which is an equatorial diastereomer of 8-substituted 3',5' cyclic adenosine monophosphorothioate (Rp-8-substituted-cAMPS), and wherein said thio-substituted cAMP analog binds to an RI α subunit of said isozyme and acts as a selective or specific antagonist of said isozyme". Support for this amendment can be found, *inter alia*, at page 5, line 20 et seq. of the present specification.

Applicants further note that the Examiner relies on Hofmann et al solely for teachings regarding restoration of T cell function in HIV infection by reduction of intracellular cAMP

AMENDMENT AFTER FINAL

U.S. Appln. No. 09/428,458

levels with adenosine analogs, and not the specific inhibitors claimed, which Hofmann et al does not teach.

It is the Examiner's position that one would have expected the instantly claimed cAMP antagonists to be useful to treat a subject in need of enhanced T cell proliferation in view of Gjertsen et al and Jastorff et al, teaching the instantly recited compounds, and Hofmann et al teaching restoration of T cell function in HIV infection by reduction of intracellular cAMP levels with adenosine analogs.

It is the Examiner's position that one skilled in the art would have been motivated to use the antagonists taught by Gjertsen et al and Jastorff et al in the same manner as taught by Hofmann et al because these compounds were known to be cAMP antagonists, and have been utilized *in vivo* by Jastorff et al.

While Hofmann et al may make a link between modulating cAMP levels and the effect of such modulation on T cell proliferation, Applicants respectfully submit that the Examiner has totally overlooked Applicants' arguments of record. That is, the observed effect when the inhibitor (ddAdo) of Hofmann et al is added to the T cells could in fact be as a result of the effect of inhibiting any one of the large number of different pathways that are affected by cAMP, or the effect could even be totally non-specific. There is no pointer in Hofmann et al towards using specific inhibitors of PKA RI α over any other available molecule that would influence cAMP signalling.

More specifically, by using ddAdo, Hofmann et al affects all cAMP pathways at their outset by affecting the levels of

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

cAMP able to initiate cAMP pathways. However, cAMP affects a myriad of different pathways, i.e., cAMP acts as a signalling molecule in pathways that are regulated by numerous hormones, neurotransmitters, cytokines, inflammatory mediators and other extracellular substances. cAMP is involved in the regulation of heart rate and contraction force, arginine-vasopressin(AVP)-induced redistribution of aquaporin-2 (AQP2) from intracellular vesicles to the plasma membrane of renal collection duct principal cells (AQP2 shuttle) leading to water reabsorption in the kidney, renin secretion from renal juxtaglomerular cells, insulin secretion from pancreatic beta-cells, acid secretion in the stomach, bronchoconstriction in the airways, fat metabolism in adipocytes, control of brain functions, steroid production in adrenal glands and gonads, cell migration and, sperm motility and a number of other processes including gene regulation and cell cycle regulation and differentiation.

Hofmann et al provides no information on which, if any, of these pathways are of relevance in affecting T cell function. Thus, Hofmann et al provides an uninformative observation that by affecting cAMP levels (or via a non-specific effect), ddAdo affects T cells. This information is too general and non-specific to be of utility in an *in vivo* situation.

As the strategy of inhibiting cAMP synthesis in Hofmann et al will affect so many pathways, it could not be put into practice *in vivo* with any reasonable expectation of success, as there would be likely many other undesirable effects on the subject.

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

Thus, Applicants respectfully submit that the Examiner's rejection is improper as such is merely an "obvious-to-try" argument, which is not a proper standard for unpatentability in the United States. Rather, there must be reasonable expectation of success for a rejection on obviousness to be soundly based.

Furthermore, Hofmann et al does not point towards the invention as claimed, since there is no motivation therein to chose an inhibitor as defined in the claims (i.e., a specific inhibitor of the PKA RI α_2 C₂ isozyme having the structural features as set out in Claim 45), which selectively inhibits a particular cAMP pathway that is not identified by Hofmann et al. There is simply no teaching from Hofmann et al that one should target upstream or downstream events relative to cAMP production.

In contrast, the present invention provides information on why affecting cAMP levels has an effect on T cells, since the relevant pathway is identified in the present application, and allows targeting of that pathway. Hofmann et al simply does not provide information on what pathway should be selected and targeted.

Moreover, in order to achieve the effects identified by Hofmann et al, the skilled person would be obliged to target the same level of the pathway, i.e., to affect adenylate cyclase activity, as employed in Hofmann et al. The Examiner has thus, made an improper conceptual leap from the disclosure in Hofmann et al that inhibiting the synthesis of cAMP affects T cells, to choosing the specifically recited PKA RI α_2 C₂ inhibitors for the same purpose, when there is no

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

motivation for doing so in Hofmann et al or in any other reference relied upon by the Examiner.

While it may be obvious to use the claimed cAMP antagonist compounds once it has been established that T cell proliferation is influenced specifically by the PKA RI α pathway, and not any of the other pathway that is influenced by cAMP, the role of PKA RI α was only identified for the first time in the present application. Without this knowledge, the skilled person has no guidance as to which of the many pathways that are under control of cAMP should be targeted in order to have an effect on T cell proliferation.

In any event, the skilled person merely would learn from Hofmann et al that if they wanted an increase T cell proliferation they could choose to administer ddAdo. This compound does not fall within the scope of the claims. As an alternative to administering ddAdo, at best, the skilled person might look in the prior art to try to identify other compounds which would have the same effect as the specific inhibitor of adenylate cyclase used by Hofmann et al, i.e., targeting the same level of the signaling cascade.

Activators and inhibitors of adenylate cyclase effect adenylate cyclase by acting:

- (i) on the G-protein to which they are coupled,
 - (ii) on the G-protein receptor,
 - (iii) on adenylate cyclase *per se*, and
 - (iv) by non-receptor-dependent mechanisms
- (see the information sheet for Calbiochem attached hereto).

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

It should be noted from the date of the references mentioned in the Calbiochem information sheet, all of these activators and inhibitors were known prior to Applicants' priority date. ddAdo is an adenylate cyclase inhibitor. Thus, a variety of different alternatives to ddAdo were known as of Applicants' priority date, and could have been tried to achieve the effects observed in Hofmann et al using alternative compounds. Hence, there are a number of different molecules (very distinct from those of the present claims) that could have been targeted to try to replicate the effect seen by Hofmann et al.

Moreover, in addition to the inhibitory molecules referred to above, the expression and/or function of the target molecules could be inhibited using antisense, antibodies or ribozymes.

The skilled person would thus, be faced with a choice of many different target molecules, and many different means of inhibiting these target molecules. There was no reasonable expectation as to which target and which means would be effective prior to the present invention.

Hofmann et al clearly does not teach the use of inhibitors which act downstream of adenylate cyclase, nor what effect such inhibitors might have. Hofmann et al is entirely silent on how the effects observed therein could be achieved by affecting the pathway at a different point. If the production of cAMP and its final effects were exerted by a single signal transduction pathway, then interference at any point along that pathway would have the same effect. However, as noted above, it is clear that cAMP is involved in a myriad of different pathways. To achieve

AMENDMENT AFTER FINAL

U.S. Appln. No. 09/428,458

the effect seen by Hofmann et al, but move to downstream inhibition, one would need to select the correct pathway. Selection of the wrong pathway would mean the effect would be lost. Hofmann et al does not teach which pathway, and thus there is no guidance on how to apply the teaching of Hofmann et al with a downstream inhibitor, even if one was motivated to do so. As such, it required the present invention to identify the relevant pathway, and thereby identify molecules which specifically targeted the pathway, and to which the claims are directed.

Even if one were to suppose that Hofmann et al teaches the downstream pathways should be targeted, which Applicants contest, a number of possible options would have presented themselves. The downstream signaling pathways diversify and the cAMP may have effects through:

- (a) cyclic nucleotide gated ion channels;
- (b) the cAMP-regulated Epac (guanine exchange factor) - Rap (small G protein) pathway; and
- (c) PKA.

Hofmann et al does not teach which, if any, of these targets should be targeted. Further, once a target was selected, appropriate inhibitors would need to be identified. Many examples of inhibitors of cyclic nucleotide gated channels exist, and were available as of Applicants' priority date. Examples include L-cis-diltiazem (see, e.g., Chen et al, *Nature*, 362:764-767 (1993)), pimozone (see, e.g., Frings et al, *J. Gen. Physiol.*, 100:45-67 (1992)), tetracaine (see, e.g., Schnetkamp et al, *J. Gen. Physiol.*, 96:517-534 (1990)), W-7, and

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

a calmodulin inhibitor (see, e.g., Kleene et al, Br. J. Pharmacol., 111:469-472 (1994)).

However, the present claims are not directed to the above-noted target or such inhibitors. Thus, the skilled person is again required to make a selection which is not taught by Hofmann et al, i.e., to target PKA.

Furthermore, while various PKA isozymes were known, Hofmann et al does not teach which one should be selected.

In addition, a variety of inhibitors were known as of Applicants' priority date for inhibiting PKA, e.g., PKI (protein), H89 (non-specific), H8 and KT5720 (which do not discriminate between different PKA isozymes) and Rp-cAMPS (which is type II selective), as well as those referred to in the claims. Hofmann et al is silent on which isozyme should be targeted and with what type of inhibitor.

If it were considered that upstream pathways could be targeted, suitable targets would include antagonists of β -adrenoreceptors (such as propranolol and many others), serotonin receptor antagonists (such as buspirone that Hofmann et al in fact published on in 1996), and histamine H2 receptor antagonists (such as cimetidine and many others), not the claimed compounds.

Thus, Hofmann et al provides only an observation about a collection of signaling pathways. No specific pathway is identified, and thus inhibitors directed exclusively to that pathway cannot be identified in Hofmann et al. This is made possible for the first time by the present invention.

AMENDMENT AFTER FINAL
U.S. Appln. No. 09/428,458

Hence, the Examiner's rejection is based on hindsight, which is legally improper.

Applicants note that the Examiner refers to Gjertsen et al as disclosing inhibiting cAMP with "cAMP antagonists". Further, in the second paragraph, on page 3 and at the top of page 5 of the Office Action, the Examiner contends that Hofmann et al teaches the use of "cAMP antagonists".

However, ddAdo used in Hofmann et al is an adenosine analogue which inhibits the enzyme adenylate cyclase so as to affect cAMP levels. ddAdo has no cAMP antagonistic or agonistic effect, and would not act directly on PKA RI α . It is thus, not a cAMP antagonist.

The Examiner contends that one would have been motivated to use the compounds taught by Jastorff et al to determine the effect on T cell function in view of Hofmann et al, particularly since Jastorff et al teaches that the R_p form is a better candidate for human therapy, since such is more resistant to hydrolysis.

In any event, while Jastorff et al may favor the R_p form, this is in preference to the S_p form. It still does not follow that this makes use of an S_p cAMP antagonist obvious since Hofmann et al does not teach the use of cAMP antagonists, but teaches the use of an inhibitor of cAMP production.

Again, Applicants respectfully submit that the Examiner's rejection is improper as such is merely an "obvious-to-try" argument, which is not a proper standard for unpatentability in the United States.

AMENDMENT AFTER FINAL

U.S. Appln. No. 09/428,458

In summary, the Examiner is using hindsight to assess inventive step, which is not appropriate, as cAMP antagonists can not be equated with molecules that inhibit cAMP production, as taught in Hofmann et al. Even if the use of cAMP antagonists had been suggested in the art, which they have not, there are many cAMP antagonists/inhibitors that would have been available to the skilled person and the Examiner has not provided any motivation in the prior art as to which particular inhibitors should be selected and which PKA isozyme should be targeted, with a reasonable expectation of success.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Gjersten et al, alone or when combined with the teachings in Hoffmann et al or Jastorff et al, and in any event such a combination can only be made in hindsight which is legally improper. Thus, Applicants request withdrawal of the Examiner's rejection.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

AMENDMENT AFTER FINAL

U.S. Appln. No. 09/428,458

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,



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